Original Article

Cerebral Small Artery Diseases may be Associated with Aortic Arch Calcification in Stroke Patients

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Aim: Aortic arch calcification (AoAC) on chest X-rays represents systemic atherosclerosis and it is associated with ischemic cardiovascular diseases. However, the relationship between ischemic stroke and AoAC has yet to be fully elucidated.

Methods: Patients with acute ischemic stroke who were undergoing chest X-ray, blood, and brain magnetic resonance imaging (MRI) examinations were prospectively studied. The extent of AoAC on chest X-ray was divided into four grades (0-3). Clinical characteristics, biochemical findings, white matter lesions on MRI, and AoAC extent were assessed in each stroke subtype, and the factors associated with AoAC were investigated.

Results: A total of 175 patients (age, 70 ± 13 years; 115 men) were enrolled in the study. According to the Trial of Org 10172 in Acute Stroke Treatment classification with minor modification, 33 patients (19%) had small artery occlusion (SAO), 42 (24%) had large artery atherosclerosis, 49 (28%) had cardioembolism, 24 (14%) had stroke with other determined etiologies, and 27 (17%) had stroke with undetermined etiologies. Compared to other stroke subtypes, the extent of AoAC was independently correlated with SAO (all $p < 0.05$). Age (odds ratio [OR]: 1.14, 95% confidence interval [CI]: 1.08 to 1.19, $p < 0.001$), hypertension, (OR: 3.44, 95% CI: 1.23 to 9.66, $p = 0.019$), diabetes mellitus (OR: 2.19, 95% CI: 0.99 to 4.85, $p = 0.054$), white matter lesions (OR: 1.54, 95% CI: 1.00 to 2.36, $p = 0.048$), and SAO (OR: 1.38, 95% CI: 1.02 to 1.89, $p = 0.040$) were significantly associated with AoAC.

Conclusions: Age, hypertension, cerebral small artery disease, and possibly diabetes mellitus appear to be closely associated with AoAC in patients with acute ischemic stroke.

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Key words: Stroke, Aortic arch calcification, Small artery disease, Stroke subtype, White matter lesions

Introduction

The presence of aortic arch calcification (AoAC) on chest X-rays indicates systemic atherosclerosis and is associated with cardiovascular events¹⁻⁴. Several atherosclerotic risk factors, including age, hypertension, cigarette smoking, and diabetes mellitus, have been shown to be associated with the development of

AoAC²⁻⁴. We previously demonstrated that high-grade AoAC was consistent with the presence of advanced atheromatous plaques in the aortic arch in patients with stroke with unknown etiologies⁵. The clinical significance of AoAC on chest X-ray to diagnose aortogenic brain embolism was shown in patients with unexplained stroke. To date, several studies have focused on the relationship between ischemic stroke and AoAC. However, little evidence exists to show that AoAC increases the risk of ischemic stroke.

According to the Trial of Org 10172 in Acute Stroke Treatment classification (TOAST), the subtypes of acute ischemic stroke include small artery occlusion (SAO), large artery atherosclerosis (LAA),

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cardioembolism (CE), stroke with other determined etiologies (OTH), and stroke with undetermined etiologies (UND)⁶. Each ischemic stroke subtype has specific atherosclerotic risk factors^{7, 8}. Hypertension and diabetes mellitus are considered traditional risk factors for SAO^{9, 10}. A previous large-scale study showed that hypertension, but not other etiologies, contributed to stroke recurrence in patients with SAO¹¹. Hypercholesterolemia was more common in SAO and LAA, and coronary artery disease and cigarette smoking were related to LAA^{7, 8}. On the other hand, white matter lesions on magnetic resonance imaging (MRI) have been associated with aging, atherosclerotic risk factors, and stroke risk¹²⁻¹⁴.

Aim

It was hypothesized that the extent of AoAC in each ischemic stroke subtype might vary among patients with different atherosclerotic risk factors. The present study analyzed the association between AoAC and stroke subtype and investigated the factors related to AoAC in patients with acute ischemic stroke.

Methods

Patient Selection

This study prospectively enrolled patients with acute ischemic stroke who were admitted to the Department of Neurology at Juntendo University Urayasu Hospital (a tertiary referral center) and the Department of Neurology at Juntendo University Hospital (a secondary referral center) between May 2012 and January 2013. Age, sex, atherosclerotic risk factors, and MRI and laboratory findings were assessed for all patients with ischemic stroke. This study proceeded in accordance with the Declaration of Helsinki. Because this was a non-invasive study, approval from the Institutional Review Board was not needed according to the local regulations.

Diagnosis of Acute Ischemic Stroke and Stroke Subtype

Brain infarction was diagnosed as an acute neurological event persisting for ≥ 24 h and associated with focal hyperintensity on diffusion-weighted imaging (DWI). All patients had chest X-rays, blood examinations, 12-lead electrocardiograms, carotid ultrasonography, brain MRI including DWI, and carotid ultrasonography within 24 h after admission, and continuous electrocardiographic monitoring was performed for at least 48 h to detect chronic or paroxysmal atrial fibrillation. In patients diagnosed with

OTH or UND on the basis of the initial stroke examinations, transesophageal echocardiography, 24-h Holter electrocardiography, three-dimensional enhanced computed tomography (CT), or cerebral angiography was performed. On the basis of the TOAST classification with minor modification^{6, 15}, stroke patients were classified into five subtypes (SAO, LAA, CE, OTH, and UND). The diagnosis of SAO was based on MRI imaging evidence of a single, clinically relevant, acute ischemic lesion ≤ 15 mm in diameter within the territory of the deep white matter, basal ganglia, or brainstem-penetrating arteries in the absence of any other pathogenesis in the parent large artery (focal atheroma, arterial dissection, vasculitis). Branch atheromatous disease (BAD) was diagnosed when infarcts were visible for more than three axial DWI cuts or 15 mm in length in each axial DWI image in the lenticulostriate or paramedian pontine arterial territory^{15, 16}. In the current study, BAD was categorized as SAO according to the previous study using the TOAST classification with minor modification¹⁵. LAA was diagnosed as the presence of either an occlusive or a $>50\%$ stenotic lesion due to atherosclerosis in the clinically relevant extra- or intracranial arteries. The diagnosis of CE included the presence of a high- or medium-risk cardiac embolic source according to the TOAST criteria with no other non-cardiac stroke pathogenesis⁶. OTH was diagnosed as the presence of a single certain stroke etiology, including arterial dissection, aortic arch atheroma with ulcerative or mobile components, Trousseau's syndrome, vasculitis, antiphospholipid syndrome, etc.⁵. The diagnosis of UND included stroke with more than two etiologies (e.g., coexistence of atrial fibrillation and corresponding arterial stenosis), stroke with incomplete investigations, and cryptogenic stroke.

Risk Factors

Vascular risk factors were assessed as follows: 1) hypertension, history of using antihypertensive agents, systolic blood pressure >140 mmHg, or diastolic blood pressure >90 mmHg at 14 days after stroke onset; 2) diabetes mellitus, use of oral hypoglycemic agents or insulin, or glycosylated hemoglobin (National Glycohemoglobin Standardization Program, NGSP) $>6.4\%$; 3) dyslipidemia, use of antihyperlipidemic agents, serum low-density lipoprotein cholesterol (LDL-C) ≥ 140 mg/dL, high-density lipoprotein cholesterol (HDL-C) <40 mg/dL, or triglyceride ≥ 150 mg/dL; 4) current smoking or history of smoking; 5) ischemic heart disease or a history of ischemic heart disease; 6) atrial fibrillation, a history of atrial fibrillation, or identification on 12-lead electrocardi-

ography and electrocardiographic monitoring; and 7) a history of peripheral artery disease.

MRI Protocol

The MRI studies included DWI, fluid-attenuated inversion recovery (FLAIR), T2-weighted images, and MR angiography (MRA) using a 1.5-Tesla MR scanner equipped with single-shot echo planar imaging (Visart/EX; Toshiba, Tokyo, Japan), resulting in a total imaging time of approximately 20 min. The diagnosis of acute infarction was based on the finding of a focal hyperintensity that was judged not to be attributable to normal anisotropic diffusion or magnetic susceptibility artifact. Periventricular hyperintensity (PVH) and deep and subcortical white matter hyperintensity (DSWMH) were defined as high-intensity lesions on axial FLAIR images according to previous studies, and they were evaluated for the extent of cerebral white matter lesions^{14, 17}. The severity of intracranial artery stenosis on MRA was defined as >50% or focal signal loss with signal reduction in the distal artery, according to the criteria of previous studies^{18, 19}. Stenoses of the bilateral intracranial carotid, anterior cerebral, middle cerebral, and posterior cerebral arteries were analyzed. MRI findings were assessed by two experienced neuroradiologists who were blinded to the patients' clinical status.

Carotid Ultrasonography

Carotid ultrasonography was performed with a LOGIC S6 (GE Medical Systems, Milwaukee, WI, USA) with a 12-MHz linear probe. All patients were examined in the supine position. The bilateral common and internal carotid arteries were examined, and >50% stenosis and carotid occlusion due to atherosclerotic plaques were diagnosed as carotid stenosis.

Chest X-Ray Study

The extent of AoAC on chest X-ray was scored as follows according to a previous study: no visible calcification (grade zero), small spots or a single thin area of calcification (grade one), one or more areas of thick calcification (grade two), and circumferential calcification (grade three, **Fig. 1**)⁴. Three experienced neurologists analyzed the extent of AoAC.

Laboratory Findings

The following covariates were also included in each model: LDL-C, HDL-C, non-HDL-C, triglyceride, apolipoprotein B, apolipoprotein A-1, NGSP, creatinine, estimated glomerular filtration rate (eGFR), high-sensitivity C-reactive protein (hs-CRP), D-dimer, calcium, and phosphorus.

Statistical Analysis

Numerical values are reported as the means $\pm$ standard deviation. Baseline characteristics, vascular risk factors, brain MRI, and laboratory findings were compared among the groups. Data were statistically analyzed using the chi-square test for categorical variables and the Mann-Whitney and Kruskal-Wallis tests for non-parametric analyses. One-way analysis of variance (ANOVA) was also used to evaluate quantitative variables to explore the differences among groups. All variables with a value of $p < 0.1$ on univariate analyses were entered into the multiple logistic regression analysis. A two-sided p value < 0.05 was considered significant. All data were analyzed using SPSS version 15.0 for Windows software (SPSS, Chicago, IL, USA).

Results

Study Population

During the study period, 162 and 95 patients with acute ischemic stroke were admitted to Juntendo University Urayasu Hospital and Juntendo University Hospital, respectively. Among these, 38 and 42 patients, respectively, were excluded due to incomplete analysis of laboratory examinations, calcium antiresorptive or calcium carbonate agent use, or dialysis due to chronic renal failure. Ultimately, 175 patients (age, 70 ± 13 years; 115 males; National Institutes of Health stroke scale [NIHSS] score, 5.7 ± 6.9) were enrolled. According to the TOAST classification with minor modification^{6, 15}, the patients were categorized into the following stroke subtypes: 33 patients (19%) as SAO, 42 (24%) as LAA, 49 (28%) as CE, 24 (14%) as OTH, and 27 (17%) as UND. In patients with SAO, 17 patients were categorized as BAD. In patients with OTH, eight had arterial dissection, 13 had aortic arch atheroma with ulcerative or mobile components, and three had Trousseau's syndrome. The UND group included 17 stroke patients with more than two etiologies, five with stroke with incomplete investigations, and five with cryptogenic stroke.

Clinical Characteristics and Laboratory Findings by Stroke Subtype

As demonstrated in **Table 1**, no significant differences were observed in age or sex among the stroke subtypes. For atherosclerotic risk factors, the frequency of dyslipidemia was significantly higher in patients with SAO than in other stroke subtypes ($p = 0.013$). Atrial fibrillation was most frequently found in patients with CE ($p < 0.001$). Patients with CE also had the highest NIHSS score, and patients with SAO had the lowest NIHSS score ($p = 0.019$).

Fig. 1. AoAC assessment.

Representative images of AoAC on postero-anterior chest radiographs are shown. The extent of AoAC is divided into four grades.

With regard to the MRI findings, no significant difference was found in the degree of white matter lesions, and patients with LAA had the highest frequency of intracranial stenosis on MRA ($p < 0.001$). The frequency of carotid stenosis was the highest in LAA, followed by UND ($p = 0.002$). **Fig. 2** shows that among stroke subtypes, the extent of AoAC was highest in patients with SAO ($p = 0.036$). **Table 2** shows laboratory data by stroke subtype. LDL-C, non-HDL-C, and apolipoprotein B levels were the highest in patients with OTH, followed by patients with SAO ($p = 0.001$). Triglyceride levels were higher in patients with UND compared to the other subtypes ($p = 0.005$). The apolipoprotein A-1 level was higher in patients with SAO than in the other subtypes ($p = 0.001$). D-dimer levels were the lowest in patients with SAO ($p = 0.008$). Patients with SAO had higher calcium and phosphorus levels compared to the other

subtypes ($p = 0.030$ and $p = 0.034$). On one-way ANOVA, the NIHSS score was higher in patients with CE than in patients with SAO ($p = 0.036$). Compared to the CE subtype, LDL-C, non-HDL-C, and apolipoprotein B levels were higher in the patients with OTH ($p < 0.001$, $p = 0.001$, $p = 0.003$) and SAO ($p = 0.010$, $p = 0.001$, $p = 0.018$). Higher levels of apolipoprotein A-1 were seen in patients with SAO compared to those with CE or UND ($p = 0.001$, $p = 0.005$), and higher levels of apolipoprotein A-1 were noted in the OTH subtype compared to CE ($p = 0.039$). D-dimer levels were lower in SAO than in OTH and UND ($p = 0.005$, $p = 0.042$), and lower in LAA than in OTH ($p = 0.028$).

Independent Factors Associated with Each Stroke Subtype

Multinomial logistic regression analysis identified

Table 1. Baseline characteristics and MRI findings of study subjects according to the ischemic stroke subtype and grade of aortic arch calcification

Characteristics	Stroke subtype						<i>p</i>
	All <i>n</i> = 175	SAO <i>n</i> = 33, 19%	LAA <i>n</i> = 42, 24%	CE <i>n</i> = 49, 28%	OTH <i>n</i> = 24, 14%	UND <i>n</i> = 27, 17%	
Sociodemographic							
Age, y [†]	70 ± 13	71 ± 12	70 ± 10	72 ± 12	67 ± 14	68 ± 15	0.447
Gender, male, no. (%)	115 (66)	19 (58)	34 (81)	31 (63)	15 (63)	16 (59)	0.196
Rsk factors, no. (%)							
Hypertension	124 (71)	23 (70)	32 (76)	31 (63)	17 (71)	21 (78)	0.628
Diabetes Mellitus	66 (38)	15 (45)	20 (48)	12 (24)	9 (38)	10 (37)	0.181
Dyslipidemia	88 (50)	22 (67)	25 (60)	15 (31)	13 (54)	13 (48)	0.013
Cigarette smoking	57 (33)	10 (30)	19 (45)	14 (29)	6 (25)	8 (30)	0.375
Coronary artery disease	28 (16)	5 (15)	4 (10)	11 (22)	3 (13)	5 (19)	0.526
Atrial fibrillation	35 (20)	3 (9)	0 (0)	27 (55)	0 (0)	5 (19)	<0.001
Peripheral artery disease	7 (4)	0 (0)	2 (5)	3 (6)	0 (0)	2 (7)	0.279
NIHSS score [†]	5.7 ± 6.9	3.8 ± 4.1	6.2 ± 8.0	8.3 ± 8.7	3.8 ± 3.8	4.4 ± 4.9	0.019
MRI findings, no (%)							
PVH	1.0 ± 1.0	1.1 ± 0.9	0.9 ± 0.8	1.2 ± 1.1	1.0 ± 1.1	0.8 ± 1.1	0.418
DSWMH	0.9 ± 0.9	0.9 ± 0.8	1.0 ± 0.7	1.1 ± 1.1	1.0 ± 1.0	0.7 ± 1.0	0.519
Intracranial arterial stenosis on MRA	56 (32)	6 (18)	29 (69)	8 (16)	5 (21)	8 (30)	<0.001
Carotid ultrasonography, no (%)							
Carotid stenosis	45 (26)	4 (12)	19 (45)	9 (18)	3 (13)	10 (37)	0.002

Characteristics	Aortic arch calcification		<i>p</i>
	Grade 0 to 1 <i>n</i> = 114, 65%	Grade 2 to 3 <i>n</i> = 61, 35%	
Sociodemographic			
Age, y [†]	66 ± 12	78 ± 8	<0.001
Gender, male, no. (%)	80 (70)	35 (57)	0.089
Rsk factors, no. (%)			
Hypertension	73 (64)	51 (84)	0.007
Diabetes Mellitus	36 (32)	30 (49)	0.022
Dyslipidemia	53 (46)	35 (57)	0.170
Cigarette smoking	42 (37)	15 (25)	0.099
Coronary artery disease	12 (11)	16 (26)	0.007
Atrial fibrillation	20 (18)	15 (25)	0.268
Peripheral artery disease	3 (3)	4 (7)	0.391
NIHSS score [†]	5.1 ± 6.0	6.9 ± 8.2	0.129
MRI findings, no (%)			
PVH	0.8 ± 0.9	1.4 ± 1.1	<0.001
DSWMH	0.8 ± 0.8	1.3 ± 1.1	0.002
Intracranial arterial stenosis on MRA	35 (31)	21 (34)	0.615
Carotid ultrasonography, no (%)			
Carotid stenosis	29 (25)	16 (26)	0.909

The Chi-square test and the Kruskal-wallis test were used for comparison. [†] mean ± SD. NIHSS=NIH Stroke scale; PVH=Periventricular hyperintensity; DSWMH=deep and subcortical white matter hyper intensity; SAO=small artery occlusion; LAA=large artery atherosclerosis; CE=cardio-embolism; OTH=stroke with other determined etiologies; UND=stroke with undetermined etiologies.

Fig. 2. AoAC scattergrams.

The degrees of AoAC in patients with SAO, LAA, CE, OTH, and UND were 1.6 ± 1.2 , 1.2 ± 1.1 , 0.9 ± 1.1 , 0.9 ± 1.0 , and 0.9 ± 1.1 , respectively. The Mann-Whitney test showed that among the five stroke subtypes, the highest degree of calcification was seen in patients with SAO ($p=0.036$).

dyslipidemia, AoAC, NIHSS score, intracranial arterial stenosis on MRA, carotid stenosis, LDL-C, non-HDL-C, triglyceride, apolipoprotein B, apolipoprotein A-1, NGSP, creatinine, eGFR, D-dimer, calcium, and phosphorus as variables to identify independent risk factors for each stroke subtype. Atrial fibrillation was eliminated from this model because it was too specific to CE and was thus considered an unanalyzable variable. The AoAC degree was independently correlated with SAO compared to LAA (odds ratio [OR]: 2.26, 95% confidence interval [CI]: 1.13 to 4.52, $p=0.021$), CE (OR: 5.06, 95% CI: 2.05 to 10.40, $p<0.001$), OTH (OR: 2.08, 95% CI: 1.01 to 4.28, $p=0.046$), and UND (OR: 2.43, 95% CI: 1.23 to 4.80, $p=0.010$; Table 3). The plasma D-dimer level was negatively associated with SAO compared to the other four stroke subtypes.

Clinical Characteristics and Laboratory Findings According to the AoAC Degree

As demonstrated in Table 1, patients with grade two to three AoAC were significantly older than those with grade zero to one AoAC ($p<0.001$). Hypertension, diabetes mellitus, and coronary artery disease were significantly more frequent in patients with grades two to three AoAC than in patients with grade zero to one AoAC ($p=0.007$, $p=0.022$, $p=0.007$). Patients with grade two to three AoAC had high degrees of PVH and DSWMH, which are indices of white matter lesions ($p<0.001$, $p=0.002$). eGFR and D-dimer levels were significantly lower in patients with grade two to three AoAC ($p=0.006$, $p=0.026$), while phosphorus levels were higher in patients with grade two to three AoAC ($p=0.015$).

Underlying Characteristics Associated with AoAC

The stepwise regression analysis included age,

Table 2. Laboratory findings in stroke patients according to the ischemic stroke subtype and grade of aortic arch calcification

Characteristics	All <i>n</i> = 175	Stroke subtype					<i>p</i>
		SAO <i>n</i> = 33, 19%	LAA <i>n</i> = 42, 24%	CE <i>n</i> = 49, 28%	OTH <i>n</i> = 24, 14%	UND <i>n</i> = 27, 17%	
Laboratory findings, mean ± SD							
LDL-C	119.6 ± 42.0	132.0 ± 37.1	118.5 ± 39.1	101.9 ± 30.9	144.5 ± 46.3	116.0 ± 51.3	0.001
HDL-C	49.2 ± 13.8	53.7 ± 19.3	49.5 ± 13.4	45.6 ± 10.5	52.2 ± 13.0	47.3 ± 11.2	0.205
non-HDL-C	144.2 ± 50.0	163.8 ± 43.6	143.5 ± 48.8	118.6 ± 38.6	168.7 ± 52.4	146.2 ± 56.3	<0.001
TG	131.5 ± 91.2	148.7 ± 85.4	129.3 ± 87.8	99.9 ± 59.6	149.3 ± 120.9	155.7 ± 109.3	0.005
Apolipoprotein B	100.9 ± 31.3	109.2 ± 30.8	101.6 ± 28.6	87.7 ± 24.4	115.4 ± 28.8	100.9 ± 40.5	0.001
Apolipoprotein A-1	134.0 ± 26.6	148.4 ± 30.4	132.6 ± 24.2	125.6 ± 24.3	144.0 ± 25.7	125.0 ± 20.8	0.001
HbA1C (NGSP)	6.1 ± 1.4	6.1 ± 1.4	6.4 ± 1.7	5.8 ± 1.0	6.4 ± 1.4	6.0 ± 1.0	0.082
Creatinine	1.0 ± 1.2	0.8 ± 0.3	1.2 ± 1.6	1.0 ± 0.7	0.7 ± 0.1	1.4 ± 2.2	0.046
eGFR	70.3 ± 24.9	72.1 ± 22.4	67.5 ± 23.5	65.2 ± 24.4	80.8 ± 18.5	72.3 ± 32.9	0.098
hs-CRP	1.1 ± 3.2	0.4 ± 0.7	0.9 ± 2.9	1.3 ± 3.2	0.6 ± 1.6	2.5 ± 5.4	0.260
D-dimer	2.1 ± 2.6	1.0 ± 0.4	1.5 ± 0.9	2.1 ± 2.3	3.5 ± 4.3	3.0 ± 3.8	0.008
Calcium	8.8 ± 0.5	9.0 ± 0.5	8.9 ± 0.6	8.8 ± 0.5	9.0 ± 0.5	8.6 ± 0.6	0.030
Phosphorus	3.0 ± 0.7	3.2 ± 0.5	2.8 ± 0.7	2.9 ± 0.6	2.8 ± 0.6	3.1 ± 0.9	0.034
Aortic arch calcification							
Characteristics	Grade 0 to 1 <i>n</i> = 114, 65%	Grade 2 to 3 <i>n</i> = 61, 35%	<i>p</i>				
Laboratory findings, mean ± SD							
LDL-C	122.3 ± 41.5	114.5 ± 42.7	0.095				
HDL-C	48.1 ± 13.9	51.2 ± 13.5	0.122				
non-HDL-C	147.6 ± 50.7	137.8 ± 48.4	0.099				
TG	141.9 ± 103.3	112.1 ± 58.8	0.116				
Apolipoprotein B	103.0 ± 31.3	97.7 ± 31.1	0.186				
Apolipoprotein A-1	133.3 ± 27.9	135.4 ± 24.2	0.511				
HbA1C (NGSP)	6.1 ± 1.4	6.2 ± 1.2	0.444				
Creatinine	1.0 ± 1.3	1.0 ± 1.1	0.555				
eGFR	73.3 ± 25.2	64.7 ± 23.5	0.006				
hs-CRP	1.3 ± 3.7	0.7 ± 1.8	0.722				
D-dimer	2.2 ± 3.1	1.9 ± 1.5	0.026				
Calcium	8.8 ± 0.6	8.9 ± 0.5	0.167				
Phosphorus	2.9 ± 0.6	3.1 ± 0.6	0.015				

The Kruskal-wallis test were used for comparison. LDL-C=low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol; eGFR=estimated glomerular filtration rate; CRP=C reactive protein; SAO=small artery occlusion; LAA=large artery atherosclerosis; CE=cardio-embolism; OTH=stroke with other determined etiologies; UND=stroke with undetermined etiologies.

sex, hypertension, diabetes mellitus, cigarette smoking, coronary artery disease, PVH, DSWMH, stroke subtype, LDL-C, non-HDL-C, eGFR, D-dimer, and phosphorus as variables to identify independent risk factors for AoAC. Age (OR: 1.14, 95% CI: 1.08 to 1.19, p <0.001), hypertension, (OR: 3.44, 95% CI: 1.23 to 9.66, p =0.019), DSWMH (OR: 1.54, 95%

CI: 1.00 to 2.36, p =0.048), and SAO (OR: 1.38, 95% CI: 1.02 to 1.89, p =0.040) were found to be independent factors for AoAC, while diabetes mellitus (OR: 2.19, 95% CI: 0.99 to 4.85, p =0.054) was non-significantly related to AoAC (**Table 4**).

Table 3. Association of underlying characteristics, MRI, and laboratory findings after multinomial logistic regression analysis in patients with stroke with other etiologies versus small artery occlusion

SAO vs LAA					
Variables	N (%) or mean $\pm$ SD		OR	95% CI	<i>p</i>
	SAO	LAA			
Aortic arch calcification	1.6 $\pm$ 1.2	1.2 $\pm$ 1.1	2.26	1.13-4.52	0.021
Carotid stenosis	4 (12)	19 (45)	0.19	0.04-0.95	0.044
Intracranial arterial stenosis	6 (18)	29 (69)	0.05	0.01-0.22	<0.001
D-dimer	1.0 $\pm$ 0.4	1.5 $\pm$ 0.9	0.19	0.05-0.70	0.013
SAO vs CE					
Variables	N (%) or mean $\pm$ SD		OR	95% CI	<i>p</i>
	SAO	CE			
Aortic arch calcification	1.6 $\pm$ 1.2	0.9 $\pm$ 1.1	5.06	2.46-10.40	<0.001
Dyslipidemia	22 (67)	15 (31)	4.85	1.13-20.84	0.034
NIHSS	3.8 $\pm$ 4.1	8.3 $\pm$ 8.7	0.82	0.69-0.97	0.024
Non-HDL-C	163.8 $\pm$ 43.6	118.6 $\pm$ 38.6	1.10	1.01-1.19	0.022
Apolipoprotein A1	148.4 $\pm$ 30.4	125.6 $\pm$ 24.3	1.03	1.01-1.06	0.018
D-dimer	1.0 $\pm$ 0.4	2.1 $\pm$ 2.3	0.14	0.04-0.52	0.003
SAO vs OTH					
Variables	Mean $\pm$ SD		OR	95% CI	<i>p</i>
	SAO	OTH			
Aortic arch calcification	1.6 $\pm$ 1.2	0.9 $\pm$ 1.0	2.08	1.01-4.28	0.046
LDL-C	132.0 $\pm$ 37.1	144.5 $\pm$ 46.3	0.92	0.85-1.00	0.046
Non-HDL-C	163.8 $\pm$ 43.6	168.7 $\pm$ 52.4	1.09	1.00-1.18	0.039
D-dimer	1.0 $\pm$ 0.4	3.5 $\pm$ 4.3	0.10	0.03-0.37	0.001
SAO vs UND					
Variables	Mean $\pm$ SD		OR	95% CI	<i>p</i>
	SAO	UND			
Aortic arch calcification	1.6 $\pm$ 1.2	0.9 $\pm$ 1.1	2.43	1.23-4.80	0.010
Apolipoprotein A1	148.4 $\pm$ 30.4	125.0 $\pm$ 20.8	1.04	1.01-1.07	0.018
D-dimer	1.0 $\pm$ 0.4	3.0 $\pm$ 3.8	0.12	0.03-0.43	0.001

OR=Odds ratio; CI=confidence interval; SAO=small artery occlusion, LAA=large artery atherosclerosis, CE=cardioembolism, OTH=other determined etiology, UND=other undetermined etiology

Discussion

Community-based and large cohort studies of patients without ischemic stroke previously showed that AoAC predicted vascular events¹⁻⁴. In the current study, patients were rigorously classified into stroke subtypes based on detailed examinations, and the relationship between AoAC and stroke subtype in patients with acute ischemic stroke was investigated. The results showed that SAO was closely associated with

AoAC. Moreover, age, hypertension, DSWMH, and possibly diabetes mellitus were associated with AoAC development in patients with acute ischemic stroke.

A population-based cohort study found that AoAC increased the risk of ischemic heart disease in men and women and ischemic stroke in women². Conversely, a few studies reported that AoAC was strongly associated with increased risks for ischemic heart disease and vascular disease but not ischemic stroke^{1, 4}. Therefore, AoAC on chest X-rays could be

an important prognostic value for patients with cardiovascular disease, whereas the relationship between AoAC and ischemic stroke remains controversial.

In the present study, both SAO and DSWMH were independent factors for AoAC development. DSWMH has been associated with cognitive impairment, risk of stroke, and personality changes^{14, 20-23}. SAO and DSWMH appear to have a common pathogenesis based on cerebral small artery disorders, including lipohyalinosis and segmental fibrinoid degeneration of the arterial walls of the perforating arteries. Therefore, SAO and DSWMH were considered cerebral small artery diseases. Complete luminal occlusion and intraluminal thrombosis in the cerebral perforating arteries have been found in the pathology of SAO, and extravasation of toxic plasma constituents into the cerebral parenchyma caused by blood-brain barrier integrity disruption has been observed in conjunction with DSWMH^{10, 24}. Recent studies revealed that DSWMH is linked with coronary and intracranial carotid artery calcification^{25, 26}. The present data indicate that development of cerebral small artery diseases is closely related to AoAC in patients with acute ischemic stroke. It is thus suggested that AoAC can be a marker of the SAO stroke subtype, as well as white matter lesions on MRI in stroke patients.

It is well known that patients with SAO are more likely to have hypertension and diabetes mellitus, while those with LAA are more likely to have dyslipidemia and coronary artery disease⁷⁻¹⁰. The current study closely investigated the relationship between the lipid profile and stroke subtype, and the data demonstrated that an abnormal lipid profile, including elevations of LDL-C, non-HDL-C, and apolipoprotein B, was more prominent in patients with OTH followed by those with SAO, but not in the LAA stroke subtype. Overall, 54% of patients with OTH were diagnosed as having aortic arch atheroma with ulcerative or mobile components, and 52% of patients with SAO were categorized as BAD. It has been shown that large aortic atheromatous plaques are associated with abnormal lipid metabolism, and BAD is more likely to be associated with dyslipidemia than lacunar infarction, which might be a cause of an abnormal lipid metabolism linked to OTH and SAO^{16, 27}. On the other hand, the present data also demonstrated that age, hypertension, and possibly diabetes mellitus, which are fundamental risk factors for SAO and DSWMH, could be associated with AoAC development in stroke patients^{13, 14}. In the Rotterdam study, advanced AoAC was related to calcification in other vessel beds, such as the carotid and coronary arteries. As a result, underlying systemic atherosclerosis might

Table 4. Association of underlying characteristics and laboratory findings with aortic arch calcification after logistic regression analysis

Variables	Odds ratio	95% CI	<i>p</i>
Age, per 1-year increase	1.14	1.08-1.19	<0.001
Hypertension	3.44	1.23-9.66	0.019
Diabetes mellitus	2.19	0.99-4.85	0.054
DSWMH	1.54	1.00-2.36	0.048
Small artery occlusion	1.38	1.02-1.89	0.040

CI = confidence interval; DSWMH = deep and subcortical white matter hyper intensity

cause systemic vascular calcification in such patients²⁸. The present data suggested an association between AoAC and cerebral small artery disease. Oxidative stress might be related to cerebral white matter diseases, and experimental studies have shown that endothelial injury and oxidative stress are implicated in the mechanisms of cerebral white matter diseases and aortic calcification²⁹⁻³¹. Therefore, AoAC and cerebral small artery disorders might have common pathogenic processes in stroke patients.

The current study has some limitations. The first is that 80 patients were excluded from the study; thus, there may have been a selection bias, which raises the issue of the generalizability of the results. Moreover, the sample size of the current study was relatively small as it was a hospital-based study. Second, the cross-sectional nature of the present study limits the interpretation of the durations of hypertension, diabetes mellitus, and dyslipidemia, and the history of medications, such as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and HMG-CoA inhibitors (statins) before stroke onset in enrolled patients. These drugs are known to suppress atherosclerosis. Third, the current study did not include control subjects, so that the contribution of AoAC to ischemic stroke was unclear. Thus, a case-control study with a much larger sample size including patients with detailed medical histories is warranted to address these issues. Fourth, peripheral artery disease was self reported or physician diagnosed, which might have led to under- or overestimation of peripheral artery disease.

Conclusion

To date, several community-based cohorts have studied the relationship between ischemic stroke and AoAC. This hospital-based study is the first to show that age, hypertension, cerebral small artery diseases,

and possibly diabetes mellitus appear to be closely associated with the development of AoAC in patients with acute ischemic stroke.

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Conflict of Interest

None.

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